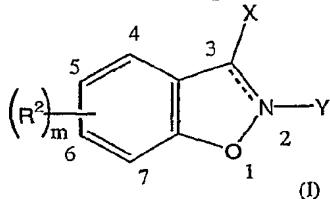


Claims

1. The use of a DAAO inhibiting compound for the manufacture of a medicament for the treatment of mental disorders, said compound having the formula



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the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

m represents an integer from 1 to 3;

10 X represents hydroxy, amino, $\text{--}\text{oxo}$ or $\text{--}\text{Z--}\text{R}^1$;

Y is absent or represents $-(C=O)-R^6$;

Z represents carbonyl, -oxy-carbonyl-, =N-carbonyl- or -NR⁵-carbonyl;

R^1 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy-, Ar^1 , Ar^2-C_{1-4} alkyl-, -NR³R⁴ or -Het¹;

15 R² represents hydrogen, halo, hydroxy, nitro, cyano, hydroxycarbonyl-, amino, mono- or di (C₁₋₄alkyl)amino-, C₁₋₆alkyloxycarbonyl-,

C₁₋₄alkyloxycarbonylC₁₋₄alkyloxy-, C₁₋₄alkyloxy- optionally substituted with one or more halo atoms or R² represents C₁₋₄alkyl optionally substituted with one or more halogen atoms;

20 R³ and R⁴ are each independently selected from hydrogen, Het², Ar³, C₁₋₄alkyl or C₁₋₄alkyl substituted with one or more substituents selected from halo, hydroxy or C₁₋₄alkyloxy-;

R^5 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonyl- or Ar^4 -carbonyl-;

25 R^6 represents a substituent selected from the group consisting of C_{1-4} alkyl,
 C_{1-4} alkyloxy-, Ar^5 , Ar^6-C_{1-4} alkyl-, - NR^7R^8 or Het^3 ;

R^7 and R^8 are each independently selected from hydrogen, Het⁴, Ar⁷, C₁₋₄alkyl or C₁₋₄alkyl substituted with one or more substituents selected from halo, hydroxy or C₁₋₄alkyloxy-;

30 Het¹ represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said heterocycle is optionally substituted with one or more substituents each independently selected from the group consisting of

amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl- and phenyl substituted with one or more halo substituents;

Het² represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or

5 benzothiazolyl wherein said heterocycle is optionally substituted with one or more substituents each independently selected from the group consisting of amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl- and phenyl substituted with one or more halo substituents;

Het³ represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or

10 benzothiazolyl wherein said heterocycle is optionally substituted with one or more substituents each independently selected from the group consisting of amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl- and phenyl substituted with one or more halo substituents;

15 Het⁴ represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or

benzothiazolyl wherein said heterocycle is optionally substituted with one or more substituents each independently selected from the group consisting of amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl- and phenyl substituted with one or more halo substituents;

20 Ar¹, Ar², Ar³, Ar⁴, Ar⁵, Ar⁶ or Ar⁷ each independently represents phenyl optionally substituted one or where possible two or more substituents selected from halo, nitro, C₁₋₄alkyl, hydroxy or C₁₋₄alkyloxy-.

25 2. The use according to claim 1 wherein for the compounds of formula (I)

m represents an integer from 1 to 3;

X represents -oxo or -Z-R¹;

Y is absent when X represents -Z-R¹ and -(C=O)-R⁶ when X represents oxo;

Z represents carbonyl, -oxy-carbonyl- or -NR⁵-carbonyl-;

30 R¹ represents C₁₋₄alkyl, Ar¹, Ar¹-C₁₋₄alkyl-, -NR³R⁴ or -Het¹;

R² represents hydrogen, halo, nitro, hydroxycarbonyl-, C₁₋₄alkyloxy or C₁₋₄alkyl;

R³ and R⁴ are each independently selected from hydrogen, Ar³ or C₁₋₄alkyl;

R⁵ represents hydrogen, C₁₋₄alkylcarbonyl- or Ar⁴-carbonyl-;

R⁶ represents a substituent selected from the group consisting of C₁₋₄alkyl, Ar⁵,

35 Ar⁶-C₁₋₄alkyl- or NR⁷R⁸;

R⁷ and R⁸ are each independently selected from hydrogen, Het⁴ or C₁₋₄alkyl;

Het¹ represents a heterocycle selected from oxazolyl, isoxazolyl, imidazolyl or pyrazolyl wherein said heterocycle is optionally substituted with one, two or three substituents selected from the group consisting of amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl, phenyl, phenyl-C₁₋₄alkyl- and phenyl substituted with one or more halo substituents, in particular said heterocycle is substituted with one or more substituents selected from the group consisting of C₁₋₄alkyl, phenyl or phenyl substituted with one or more halo substituents; in a particular embodiment Het¹ represents a heterocycle selected from isoxazolyl and pyrazolyl wherein said heterocycle is substituted with one or more substituents selected from the group consisting of amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl, phenyl, phenyl-C₁₋₄alkyl- and phenyl substituted with one or more halo substituents, in particular said heterocycle is substituted with one or more substituents selected from the group consisting of C₁₋₄alkyl, phenyl or phenyl substituted with one or more halo substituents;

Het⁴ represents a heterocycle selected from oxazolyl or isoxazolyl, wherein said heterocycle is optionally substituted with one or more substituents selected from the group consisting of amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl and phenyl substituted with one or more halo substituents, in particular said heterocycle is substituted with one or more substituents selected from C₁₋₄alkyl, phenyl or phenyl substituted with one or more halo substituents; in a particular embodiment Het⁴ represents isoxazolyl substituted with one or more substituents selected from C₁₋₄alkyl, phenyl or phenyl substituted with one or more halo substituents;

Ar¹, Ar², Ar³, Ar⁴, Ar⁵ or Ar⁶ each independently represents phenyl;

3. A compound of formula (I) a defined in claims 1 or 2, provided however that when;

- Z is -oxycarbonyl and R¹ is chloro- or nitro-phenyl-, then R² is not methyloxy-, ethyloxy-, chloro or fluoro,
- Z is -oxycarbonyl and R¹ is methyl, methyloxy-, ethyloxy-, phenyl, chlorophenyl, nitrophenyl, isoxazolyl substituted with chloro or methyl or when R¹ is pyrazolyl substituted with ethyl and methyl, then R² is not hydrogen, chloro, fluoro, bromo, ethyloxy, methyloxy or methyl,
- Z is -NR⁵-carbonyl and R¹ is methyl, methyloxy-, ethyloxy-, t-butyloxy-, benzyloxy-, phenyl or di-chlorophenyl, then R² is not hydrogen, halo, methyl or trifluoromethyl, or

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- Z is oxycarbonyl and R³ or R⁴ is a methyl, isopropyl, propyl, t-butyl or an isoxazolyl substituted with either chloro, one methyl substituent or with one methyl and one di-chloro-phenyl substituent, then R² is not hydrogen, chloro or methyl.

5

4. A compound of formula (I) wherein R^1 is a heterocycle Het¹ selected from the group consisting of isoxazolyl, pyrazolyl or benzisoxazolyl wherein said Het¹ is optionally substituted with one or more substituents each independently selected from the group consisting of C₁₋₄alkyl, phenyl and phenyl substituted with one or more halo substituents,
10 provided that when R^1 is a substituted isoxazolyl or a substituted pyrazolyl, then R^2 is not hydrogen, chloro or methyl.

15

5. A compound of formula (I) as claimed in claims 3 or 4, for use as a medicine.

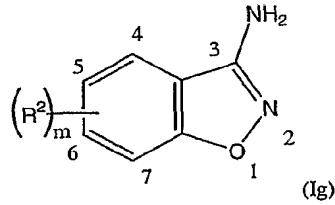
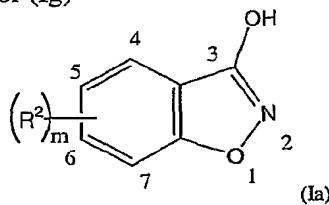
6. Use of a compound of formula (I) as claimed in any of claims 1 to 4 in the manufacture of a medicament for the treatment of schizophrenia.

20

7. A method of treating a mental disorder such as schizophrenia, the method comprising administering to an animal in need of such treatment a therapeutically effective amount of a compound of formula (I).

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8. The use of intermediates with DAAO inhibiting activity in the manufacture of a medicament for treatment of mental disorders, said intermediates having formula (Ia) or (Ig)



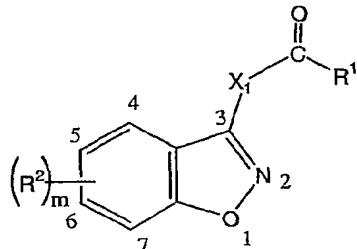
the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

30 m represents an integer from 1 to 3;
R² represents hydrogen, halo, hydroxy, nitro, cyano, hydroxycarbonyl-, amino,
mono- or di (C₁₋₄alkyl)amino-, C₁₋₆alkyloxycarbonyl-,
C₁₋₄alkyloxycarbonylC₁₋₄alkyloxy-, C₁₋₄alkyloxy- optionally substituted with

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one or more halo atoms or R² represents C₁₋₄alkyl optionally substituted with one or more halogen atoms.

9. A compound of formula



(Ic)

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the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

10

m represents an integer from 1 to 3;

X₁ represents O or NR⁵;

R¹ represents C₁₋₄alkyl, C₁₋₄alkyloxy-, Ar¹, Ar²-C₁₋₄alkyl-, -NR³R⁴ or Het¹;

15

R² represents hydrogen, halo, hydroxy, nitro, hydroxycarbonyl-, amino, mono- or di (C₁₋₄alkyl)amino, C₁₋₆alkyloxycarbonyl-,

C₁₋₄alkyloxycarbonylC₁₋₄alkyloxy-, C₁₋₄alkyloxy- optionally substituted with one or more halo atoms or R² represents C₁₋₄alkyl optionally substituted with one or more halogen atoms;

20

R³ and R⁴ are each independently selected from hydrogen, Het², phenyl, C₁₋₄alkyl or C₁₋₄alkyl substituted with one or more substituents selected from halo, hydroxyl, phenyl or C₁₋₄alkyloxy-;

25

R⁵ represents hydrogen, C₁₋₄alkyl, phenyl-carbonyl- or C₁₋₄alkyl-carbonyl-;

Het¹ represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said heterocycle is optionally substituted with one or more substituents each independently selected from the group consisting of amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl- and phenyl substituted with one or more halo substituents;

30

Het² represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said heterocycle is optionally substituted with one or more substituents each independently selected from the group consisting of

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amino, C_{1-4} alkyl, hydroxy- C_{1-4} alkyl-, phenyl, phenyl- C_{1-4} alkyl- and phenyl substituted with one or more halo substituents,

provided that when;

- X_1 is -O- and R^1 is methyl, methyloxy-, ethyloxy-, phenyl, chlorophenyl, 5 nitrophenyl, isoxazolyl substituted with chloro or methyl or when R^1 is pyrazolyl substituted with ethyl and methyl, then R^2 is not hydrogen, chloro, fluoro, bromo or methyl,
- X_1 is NR^5 and R^1 is methyl, methyloxy-, ethyloxy-, t-butyloxy-, benzyloxy-, 10 phenyl or di-chloro-phenyl, then R^2 is not hydrogen, halo, methyl or trifluoromethyl,
- X_1 is -O- and R^3 or R^4 is a methyl, isopropyl, propyl, t-butyl or an isoxazolyl substituted with either chloro, one methyl substituent or with one methyl and one di-chloro-phenyl substituent, then R^2 is not hydrogen, chloro or methyl.

15 10. A compound according to claim 9 wherein

m is 1;

X_1 represents O or NR^5 ;

R^1 is NR^3R^4 or Het^1 ;

R^2 is hydrogen, halo or R^2 represents C_{1-4} alkyl;

20 R^3 and R^4 are each independently selected from hydrogen, Het^2 and C_{1-4} alkyl;

R^5 represents hydrogen or C_{1-4} alkyl-carbonyl-;

Het^1 is isoxazolyl or imidazolyl each independently substituted with one or more substituents selected from C_{1-4} alkyl and phenyl substituted with one or more halo substituents;

25 Het^2 is isoxazolyl substituted with one or more substituents selected from C_{1-4} alkyl and phenyl substituted with one or more halo substituents.

11. A compound according to claim 9 wherein

m is 1;

30 X_1 represents NR^5 ;

R^1 is NR^3R^4 or Het^1 ;

R^2 is hydrogen, chloro or methyl;

R^3 represents hydrogen and R^4 is C_{1-4} alkyl, phenyl or C_{1-4} alkyl substituted with phenyl;

35 R^5 represents hydrogen, phenyl-carbonyl- or C_{1-4} alkyl-carbonyl-;

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Het¹ is isoxazolyl or imidazolyl each independently substituted with one or more substituents selected from C₁₋₄alkyl and phenyl substituted with one or more halo substituents;

Het² is isoxazolyl substituted with one or more substituents selected from C₁₋₄alkyl
5 and phenyl substituted with one or more halo substituents.

12. A compound according to claim 9 wherein X₁ represents O and R³ and R⁴ are each independently selected from Het², Ar³, C₁₋₄alkyl or C₁₋₄alkyl substituted with one or more substituents selected from halo, hydroxy or C₁₋₄alkyloxy-.

10

13. A compound according to any of claims 9 to 12 for use as a medicine.

14. Use of a compound of formula (Ic) in the manufacture of a medicament for treating mental disorders such as schizophrenia.

15

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, an effective DAAO inhibitory amount of a compound as described in any one of the claims 3, 4 or 9 to 12.

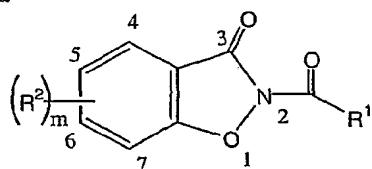
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16. A method of treating a mental disorder such as schizophrenia, the method comprising administering to an animal in need of such treatment a therapeutically effective amount of a compound of formula (I).

25

17. A method of treating a mental disorder such as schizophrenia, the method comprising administering to an animal in need of such treatment a therapeutically effective amount of an intermediate of formula (Ia) or (Ig).

18. A compound of formula



(Id)

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the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

m represents an integer from 0 to 3;

R¹ represents hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxy, Ar¹, Ar²-C₁₋₄alkyl, NR³R⁴ or Het¹;

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R² represents hydrogen, halo, hydroxy, nitro, cyano, hydroxycarbonyl-, amino, mono- or di (C₁₋₄alkyl)amino, C₁₋₆alkyloxycarbonyl-, C₁₋₄alkyloxycarbonylC₁₋₄alkyloxy-, C₁₋₄alkyloxy- optionally substituted with one or more halo atoms or R² represents C₁₋₄alkyl- optionally substituted with one or more halogen atoms;

5 R³ and R⁴ are each independently selected from hydrogen, Het², Ar³, C₁₋₄alkyl or C₁₋₄alkyl substituted with one or more substituents selected from halo, hydroxy or C₁₋₄alkyloxy-;

Het¹ represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said Het¹ is optionally substituted with one or more substituents each independently selected from the group consisting of amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl- and phenyl substituted with one or more halo substituents;

10 Het² represents a heterocycle selected from oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, benzisoxazolyl, benzimidazolyl or benzothiazolyl wherein said Het¹ is optionally substituted with one or more substituents each independently selected from the group consisting of amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl- and phenyl substituted with one or more halo substituents;

15 Ar¹, Ar² or Ar³ each independently represents phenyl optionally substituted one or where possible two or more substituents selected from halo, nitro, C₁₋₄alkyl, hydroxy or C₁₋₄alkyloxy.

20 provided that when:

25 - m represents 1 and R¹ represents chloro- or nitro-phenyl, then R² is not hydrogen, methoxy, ethoxy, chloro or fluoro;

- R¹ represents ethoxy or methoxy, then R² is not hydrogen, bromo, fluoro or chloro;

- R¹ represents methyl, then R² is not hydrogen, bromo or chloro.

30

19. A compound of formula (Id) for use as a medicine.

20. Use of a compound of formula (Id) in the manufacture of a medicament for treating mental disorders such as schizophrenia.

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21. A method of treating a mental disorder such as schizophrenia, the method comprising administering to an animal in need of such treatment a therapeutically effective amount of an intermediate of formula (Id).